



**Karolinska  
Institutet**

**Institutionen för klinisk neurovetenskap**

# Genetic regulation of neuroinflammation after infection and injury

**AKADEMISK AVHANDLING**

som för avläggande av medicine doktorsexamen vid Karolinska  
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av

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## ABSTRACT

Neuroinflammation is a common theme in a spectrum of central nervous system (CNS) diseases resulting in neuronal damage and degeneration. The exact mechanisms regulating inflammation in the CNS or its consequences in terms of nerve injury are still not known in detail. However, it is known that many inflammatory conditions at least in part are regulated by genetic factors. Exact definition of these factors will provide a better understanding of underlying mechanisms. The focus of this thesis has been to explore the genetic regulation of neuroinflammation in viral infections and mechanical nerve injuries using experimental models.

The genetic regulation of susceptibility to *Herpes simplex type-1* encephalitis (HSE), a devastating condition that affects humans, was investigated in different inbred rat strains. Using a series of different experimental approaches we succeeded in defining two different candidate genes that regulate susceptibility to HSE. Interestingly, these genetic influences act at two different stages of neurotropic HSV-1 virus CNS entry. Thus, the calcitonin receptor (*Calcr*) gene was identified as a candidate for peripheral neuronal infection and propagation to the CNS, while the von Willebrand factor (*Vwf*) gene was identified as a candidate for disease progression in the CNS and blood-brain barrier (BBB) dysfunction. The latter has previously been associated to cerebral malaria infection by *Plasmodium falciparum* and endothelial cell activation, suggesting that this gene is important in several human infectious conditions. More detailed histopathological and molecular studies of HSV-1 propagation, immune cell recruitment and inflammatory changes was the focus of another study, which provides further support for the notion that entry of virus into the perineurium is an important step regulating susceptibility for virus propagation into the CNS. Also, the differences found between the studied strains in relation to immune activation and responses in the peripheral nervous system (PNS) and CNS clearly demonstrate that genetic factors regulate virus - host interactions. Thus, our studies on HSE have provided several new perspectives of how susceptibility to HSV-1 virus can be regulated at different levels, as well as identifying two different candidate genes, all of which can serve as basis for further studies of human HSE.

In a fourth study, the genetic regulation of the response to a mechanical nerve injury was explored in order to identify regulatory pathways for innate immune responses occurring without an infectious trigger. We identified two quantitative trait loci (QTLs) on chromosome 1 (*Neuinflam4*) and 7 (*Neuinflam5*), respectively, regulating major histocompatibility complex class II (MHC II) expression after ventral root avulsion. Additionally, another QTL (*Neuinflam9*) on chromosome 10 regulated the expression of several important innate immune genes, including *C1q*, *Il1b*, *Tlr2* and *Irf7*. The chromosome 10 region containing *Neuinflam9* overlaps with *Toxo1*, which regulates resistance to *Toxoplasma gondii* infection. Interestingly, a part of this QTL conferred resistance to experimental autoimmune encephalomyelitis (EAE), an animal model for multiple sclerosis (MS) indicating that this QTL could regulate susceptibility both to infectious and autoimmune conditions.

In conclusion, the identification of several genetically regulated pathways presented herein provides a basis for further molecular exploration of different conditions characterized by neuroinflammation. This will be a necessary prerequisite for the formulation of new targeted therapeutic interventions that can prevent permanent damage to the nervous system.